REMARKS

Claims 1-35 are active. Claims 1, 2, 8, 17-18, 20, 23, 25, 29, and 31 have been amended. New claims 32-35 have been added.

Claim 1 has been amended to recite "inner membrane comprising" in step (a) (instead of "inner membrane of"). Support may be found at page 7, paragraph [0017] (particularly lines 3-4 and 9-10 of that paragraph). Claim 1 has also been amended to delete the limitations "disintegrant" in step (c) and "the tablet rapidly disperses into granules on contact with water," supported by claim 1 as originally filed. The "disintegrant" limitation is present in claim 2, and the members of the Markush group have been moved to new claim 32.

Claim 20 has been amended to delete the term "compressible coated potassium chloride" preceding "microcapsules" for clarity. Applicants submit that this amendment does not broaden the scope of the claim or introduce new matter because they are redundant with limitations already in the claim. Claim 20 has also been amended to delete the limitation "the tablet rapidly disperses into granules on contact with water," supported by claim 20 as originally filed.

Claim 25 has been amended to include a Markush group of disintegrants. Support may be found at paragraph [0025], page 10 of the specification.

New claim 33 has been added to recite a tablet comprising a disintegrant and optionally a surfactant, substantially free of lubricants. Support may be found at paragraph [0009], page 5 and the examples of the specification. New claims 34 and 35 have been added, directed to the plasticizer in the outer coating of the microcapsules in the controlled release potassium chloride tablet. Support may be found at page 8, paragraph [0020] of the specification.

Claims 8, 17-18, 20, 23, 29, and 31 have been amended to correct grammatical and typographical errors.

Applicants submit that no new matter has been added by these amendments.

Applicants thank the Examiner for entering the amendments in the reply filed January 4, 2008.

I. Rejection under 35 U.S.C. § 103(a) over Gantt in view of Bins

The Examiner has rejected claims 1-5, 7-27, and 29-31 over WO 01/43725 A1 to Gantt et al. in view of U.S. Patent No. 4,777,044 to Bins. Applicants respectfully traverse the rejection.

First, the combination of Gantt and Bins fails to properly support *prima facie* obviousness because the combination lacks any disclosure of tablets having ≤ 0.3% friability as in the present claims. Specifically, Bins is silent on friability values, and Gantt merely mentions that certain tablets have "low friability" without reporting values.[1] The Examiner provides no other evidence or knowledge in the art suggesting the claimed friability, and even if, *arguendo*, Gantt's or Bins's tablets inherently disclosed the claimed friability values, an obviousness rejection cannot be predicated on a property inherent or unknown at the time of the invention. MPEP § 2141.02. Applicants note that the friability of the claimed tablets, and provided by the claimed process, affords improved tablet strength and resistance to abrasion and attrition during transport and storage.[2]

Second, the Examiner uses an improper hindsight analysis by combining Gantt and Bins to arrive at the claimed invention.

Applicants' claimed tablet comprises a potassium chloride crystal surrounded by two distinct layers (an inner layer of ethylcellulose and an outer layer of plasticized polymer) to form a microcapsule. These microcapsules are mixed with microcrystalline cellulose and colloidal silicon dioxide, and the mixture is compressed into a tablet. The colloidal silicon dioxide provides superior hardness and friability properties compared to otherwise substantially identical tablets without colloidal silicon dioxide.[3]

Gantt also teaches controlled-release potassium chloride tablets, but Gantt's tablets do not contain colloidal silicon dioxide, as the Examiner acknowledges.[4]

The Examiner relies on Bins to cure this deficiency in Gantt. Bins includes colloidal silicon dioxide in the compression mixture of a compressed tablet of ammonium nitrate. Unlike Gantt, Bins's tablet does not contain microcapsules, but rather an unstructured drug/excipient

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[1] Page 5, lines 12-13.
[2] *See* page 12, para. [0030] of Applicants' specification.
[3] *Compare* Examples 10-13 with Examples 3-6, and see discussion of unexpected results below.
[4] Office Action at 3.

compression mix. The only polymeric layer taught in Bins coats the outside of the tablet. Bins's preferred tablet-coating polymers contain carboxylate moieties that immediately dissolve in the intestine[5] and remain intact in the stomach.[6]

Bins and Gantt disclose numerous components in their respective tablets, allowing for numerous combinations, the vast majority of which would not provide the claimed invention. For example, one skilled in the art could just as readily incorporate the potassium chloride crystals of Gantt directly into the compression mixture as taught by Bins, then singly coat the final tablet with Bins's preferred enteric polymer. Or the skilled artisan might choose the dual coating from Gantt's microcapsules and apply it outside the Bins-inspired tablet. In either case, the resulting combination would not provide the claimed tablet because neither combination would contain Gantt's dual-coated microcapsules. Since neither Bins nor Gantt provides sufficient direction to make the specific combination suggested by the Examiner, only the benefit of hindsight informed by Applicants' disclosure would reasonably prompt the Examiner's proposed modification to incorporate Bins's colloidal silicon dioxide into Gantt's compression mixture, while ignoring Bins's other preferred teachings (e.g., controlled-release coating on the outside of the tablet).

Applicants note that these Bins-inspired modifications to Gantt would be expected to sacrifice many of the benefits of the claimed invention. For instance, incorporating Gantt's potassium chloride crystals into Bins's tablet coated with an enteric polymer (i.e., swapping KCl for ammonium nitrate) would result in immediate release of potassium chloride as soon as the tablet entered into the intestine. This combination would provide a delayed, immediate release of potassium chloride, along with the well-known side effects of gastrointestinal irritation, purging, weakness, and circulatory disturbances.[7] The second combination mentioned above (coating a Bins-styled tablet with the dual coating on Gantt's microcapsule) would reasonably be

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[5] *See* col. 2, ll. 25-28 ("particularly cellulose acetopriopionate") and the Example (Eudragit L). Bins's tablet disintegrates rapidly at intestinal pH (pH 7.5), after 6-7 minutes (col. 3, ll. 9-12).
[6] Drug release from Bins's tablet at gastric pH (pH 1.2) is slow (1 hour).
[7] *See* column 2, lines 1-3 of US 4,863,743 to Hsiao et al., incorporated into the present specification by reference.

expected to result in localized release of potassium chloride in the intestine and cause gastric irritation.[8]

Thus, numerous possible combinations of Gantt and Bins would not result in the claimed process or tablet, and, indeed, the references' preferred teachings would point one of ordinary skill in the art toward processes or tablets quite different from those presently claimed. Only hindsight informed by Applicants' disclosure would reasonably prompt the Examiner's proposed combination. Accordingly, the rejection over Gantt in view of Bins is improper, and Applicants respectfully request that it be withdrawn.

Claims 16, 27, and 33: Bins Teaches Away from "Substantially Free of Lubricants"

Applicants note that Bins teaches away from the composition of instant claims 16, 27, and 33, which recite that the compressible blend or tablet is "substantially free of lubricants." Bins's preferred teaching incorporates "a lubricating agent e.g. magnesium stearate."[9] Bins further teaches that "[p]referably one should start from" this lubricant mixture, reasonably suggesting that a conventional tablet lubricating agent such as magnesium stearate should always be included. Gantt does nothing to discredit Bins's teaching away, as Gantt likewise teaches that lubricating agents can be used in the tablet.[10]

The Examiner had previously taken the position that claims 16 and 27 are not separately patentable because they supposedly are "contradicting to the subject matter of claims 1 and 20," the claims from which they depend.[11] According to the Examiner, the compositions of claim 16 and 27 cannot be "substantially free of lubricant" because they include the "silicon dioxide" of claims 1 and 20. The Examiner apparently interpreted "lubricant" in the present claims to encompass silicon dioxide and pointed to two references (Gilinski and Chiodini)[12] listing "silicon dioxide" as examples of lubricants. According to the Examiner, these references established that "it is well known in pharmaceutical art that silicon dioxide is useful as a lubricant."[13]

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[8] *See* page 9, para. [0023] of the present specification.
[9] Col. 1, l. 67-col. 2, l. 7; *see also* Bins's sole example, incorporating magnesium stearate.
[10] Page 4, lines 25-28.
[11] Office Action dated February 13, 2007, pages 5-6.
[12] US 2006/0222699 to Gilinski and US 4,895,836 to Chiodini et al.
[13] Office Action dated February 13, 2007, pages 5-6.

Applicants disagree with the Examiner's interpretation of "lubricant" in claims 16 and 27. First, present claims 1 and 20 recite "colloidal silicon dioxide," not "silicon dioxide," and neither Gilinski nor Chiodini mentions colloidal silicon dioxide. As previously noted by Applicants, colloidal and non-colloidal silica have significantly different particle sizes, resulting in different properties,[14] and the Examiner has not provided any evidence to establish that colloidal silicon dioxide is known in the art as a lubricant; nor has the Examiner provided a basis for assuming that a property attributed to non-colloidal silica (e.g., lubricating ability) corresponds to colloidal silica as well.

Second, Applicants note that colloidal silicon dioxide is referred to as a glidant in the present specification[15] and is distinguished from conventional lubricants such as magnesium stearate (e.g., a glidant is used "instead of a widely used lubricant such as magnesium stearate"[16]). It would thus be inconsistent with the present specification to interpret the term "lubricant" to encompass the glidant colloidal silicon dioxide when the specification states that a glidant is used instead of a lubricant. (*See* MPEP § 2111, which states, "During patent examination, the pending claims must be given their broadest reasonable interpretation consistent with the specification." (emphasis added); M.P.E.P. § 2111.01 (IV), which states "The specification should be relied on for . . . the meaning of a particular claim term [] defined by implication; that is, according to the usage of the term in the context in the specification." (emphasis added))

Therefore, Applicants submit that the Examiner's rejection of claims 16 and 27 for "contradicting" their respective independent claims, is improper, and Applicants respectfully request that it be withdrawn.

II. Rejection under 35 U.S.C. § 103(a) over Gantt in view of Vilkov

The Examiner has rejected claims 1-5, 7-27, and 29-31 over WO 01/43725 A1 to Gantt et al. in view of U.S. Patent No. 5,807,579 to Vilkov. Applicants respectfully traverse this rejection.

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[14] *See* Reply dated January 4, 2008, page 8, footnote 1.
[15] Specification, page 3, para. [0004].
[16] Specification, page 5, para. [0006] (emphasis added).

First, the combination of Gantt and Vilkov fails to teach ≤ 0.3% tablet friability. Vilkov is silent on tablet friability, and, as discussed above, Gantt merely mentions "low friability" without reporting values.[17] The Examiner provides no other evidence or common knowledge in the art to account for the claimed friability, and even if, *arguendo*, Gantt's or Vilkov's tablets inherently disclosed the claimed friability values, an obviousness rejection cannot be predicated on a property inherent or unknown at the time of the invention. MPEP § 2141.02. Applicants note that the friability of the claimed tablets, and provided by the claimed process, affords improved tablet strength and resistance to abrasion and attrition during transport and storage.[18]

Second, even if the references combined taught the claimed friability, the Examiner uses an improper hindsight analysis by combining Gantt and Vilkov to arrive at the claimed invention.

Vilkov teaches a tablet containing extended-release pseudoephedrine pellets and a second drug that is released immediately. Vilkov's preferred and "especially preferred" tablet mixtures list the ingredients powdered cellulose, a carbonate or bicarbonate, corn starch, and magnesium stearate, but no silicon dioxide (colloidal or otherwise).[19] Vilkov includes colloidal silicon dioxide in only one example (Example 1), where it is present in a tablet mixture without microcrystalline cellulose[20] and with the lubricant magnesium stearate. Vilkov does not identify any special purpose of colloidal silicon dioxide.[21] Microcrystalline cellulose is included in the pellet core but not in the compression blend for tableting.[22] In addition, Vilkov offers three methods to improve

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[17] Page 5, lines 12-13.
[18] *See* page 12, para. [0030] of Applicants' specification.
[19] Col. 3, ll. 13-21; col 3, ll. 60-65.
[20] Example 1 of Vilkov (the only example including colloidal silicon dioxide) does not contain any microcrystalline cellulose, but it does contain powdered cellulose in the drug granules. Powdered cellulose differs structurally from microcrystalline cellulose. Powdered cellulose is prepared by mechanically micropulverizing cellulose. Microcrystalline cellulose is prepared by partially hydrolyzing cellulose with mineral acid. These structural differences provide different properties, as powdered cellulose is amorphous and microcrystalline cellulose is highly crystalline. *See* AAPS PharmSci 2003; 5 (4) Article 31 (especially first paragraph under "Introduction"), describing differences of powdered vs. microcrystalline cellulose, available at http://www.aapsj.org/articles/ps0504/ps050431/ps050431.pdf, a copy of which is submitted with this Reply.
[21] Vilkov identifies silicon dioxide as a glidant and a filler (col. 3, l. 37 and col. 4, ll. 40-42) but does not identify any properties associated with colloidal silicon dioxide.
[22] Col. 3, ll. 60-65.

the compressibility properties of the extended-release pellets, one of which suggests incorporating microcrystalline cellulose but not colloidal silicon dioxide.[23]

Gantt and Vilkov each have numerous teachings, and the vast majority of their possible combinations do not provide the claimed tablet or process. For example, one of ordinary skill in the art might reasonably combine Vilkov's preferred or especially preferred tablet mixture with the microcapsules of Gantt, which would not include either colloidal silicon dioxide or microcrystalline cellulose and thus would not provide the claimed compressible blend or tablet. Or, if the skilled artisan wanted to improve the compressibility, the skilled artisan would reasonably be expected to follow Volkov's three express teachings to modify the manufacturing process accordingly, one of which would include microcrystalline cellulose but not colloidal silicon dioxide. Thus Applicants submit that Vilkov's preferred and express teachings might reasonably lead one of ordinary skill in the art to modify Gantt to produce a tablet without colloidal silicon dioxide and perhaps without microcrystalline cellulose.

To reach the Examiner's proposed combination, one of ordinary skill in the art would have to look past Vilkov's preferred and "especially preferred" tablet mixtures, pluck an individual ingredient for which no special purpose is identified (colloidal silicon dioxide) from a non-preferred tablet mixture, leave behind the lubricant (magnesium stearate) from that same tablet mixture, select an ingredient used in the pellet core (microcrystalline cellulose) and use it instead in the compression mixture, and combine them with the compression blend and microcapsules of Gantt's tablet. It is well settled that a reference disclosing a broad genus must provide some guidance to select the claimed species to render that species obvious; e.g., an express teaching or a teaching of a "preferred" species.[24] Vilkov provides no teaching for selecting colloidal silicon dioxide at all, and certainly no guidance for combining it with microcrystalline cellulose. Nor does Vilkov provide any teaching for selecting microcrystalline cellulose an ingredient in the drug granules and moving to other components of Vilkov's tablet. Without any guidance provided by either reference, it could not have been obvious to select the mismatched, non-preferred ingredients of Vilkov and incorporate them into Gantt's tablet. Only

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[23] Col. 4, l. 55-col. 5, l. 13.
[24] *See* MPEP § 2144.08(II)(4) (*citing In re Deuel*, 51 F.3d 1552, 1558 (Fed. Cir. 1995)).

hindsight informed by Applicants' disclosure would reasonably prompt the Examiner's proposed combination.

Accordingly, the rejection under Section 103 over Gantt in view of Vilkov is improper, and Applicants respectfully request that it be withdrawn.

III. Rebuttal of *Prima Facie* Case: Unexpected Results Established by Comparative Tests

Even if the Examiner had established a *prima facie* case of obviousness, Applicants submit that it is rebutted by evidence of superior or unexpected results in the specification. MPEP § 2145. Evidence of criticality or unexpected results must be considered as objective evidence of nonobviousness, and "Examiners must consider comparative data in the specification intended to illustrate the claimed invention in reaching a conclusion with regard to the obviousness of the claims." MPEP § 716.01(a) (emphasis added).

Applicants' specification contains comparative data illustrating:

- superior and/or unexpected friability of tablets containing colloidal silicon dioxide in the compression blend or tablet, compared to tablets without colloidal silicon dioxide (establishing nonobviousness of claims 1-35); and
- superior and/or unexpected hardness and friability of tablets containing colloidal silicon dioxide and substantially free of lubricants, compared to tablets without colloidal silicon and with a lubricant (further establishing nonobviousness claims 16, 27, and 33).

Nonobviousness of Claims 1-35

Applicants direct the Examiner's attention to Example 10 in the specification, which contains colloidal silicon dioxide in the compression blend and has a friability value of 0.1%. In comparison, Examples 4-6, which lack colloidal silicon dioxide but otherwise contain the same ingredients, show friability values ranging from 0.9% to 1.6%. (See Table 1 below.) Thus the tablet of Example 10 incorporating colloidal silicon dioxide exhibits 9-16 times improved friability. The superior friability attributable to colloidal silicon dioxide in the compression

blend is significant because low-friability tablets better resist abrasion and attrition during transportation and storage.[25] Thus Applicants submit that the comparative data in the specification showing the criticality of the colloidal silicon dioxide in the compression blend or tablet rebuts the Examiner's position that the processes or tablets of claims 1-35 are obvious.

Table 1:
Comparison of Tablets/Compressible Blends With and Without Colloidal Silicon Dioxide

	Example 4*	Example 5*	Example 6*	Example 10
First coating polymer	ethylcellulose	ethylcellulose	ethylcellulose	ethylcellulose
Compressible coating: Plasticized Polymer	PVP + DBS	PVP + DBS	PVP + DBS	PVP + DBS
Additional ingredients in compressible blend	MCC	MCC	MCC	Colloidal SiO_2; MCC
Friability	1.5%	1.6%	0.9%	0.1%

* The tablets of Examples 4 and 5 are scored. The tablet of Example 6 is unscored.

Applicants note that although the comparative data in the specification is not identical to Gantt, the comparative examples in the specification are reasonably more closely related to the claimed tablets than those of Gantt (presumably what the Examiner considers to be the closest prior art record). (Applicants further note that such a comparison is permissible under MPEP § 716.02(e)(I)). As such, the comparative examples of the present specification would reasonably provide a more stringent comparison to the claimed compositions and processes than with those of Gantt.[26] Here, the comparative Examples 4-6 in the present specification differ from inventive Example 10 by a single ingredient (colloidal silicon dioxide), whereas Examples 4 and 6 of Gantt differ from Example 10 by colloidal silicon dioxide and an additional ingredient; for example, the plasticizer or an additional polymer in the compressible coating.[27] And the remaining examples of Gantt (Examples 1-3 and 5) differ from any one of the present inventive Examples 10-13 by

[25] Specification, page 12, para. [0030].
[26] Applicants note that Gantt does not report friability or hardness values of the tablets disclosed therein.
[27] Examples 4-6 of the present specification are identical to Examples 4 and 6 of Gantt, except that in the compressible coating Gantt uses a different plasticizer, as in Example 4 (Gantt uses the plasticizer mix is PEG400/PEG4000, compared to DBS in Examples 4-5 of the present specification), or additional polymer, as in Example 6 (Gantt incorporates an additional polymer (Ethocel® (ethylcellulose)).

colloidal silicon dioxide and at least two ingredients; for example, the plasticizer and/or polymer(s) in the compressible coating, and/or the disintegrant and/or lubricant in the compressible blend.

Because the comparative examples in the present specification are even more similar to the claimed tablets and processes than those of Gantt, the ~9-16-fold improvement reported in the comparisons of the present specification would reasonably be even greater if a direct comparison was made to the tablets/processes of Gantt. Accordingly, Applicants respectfully submit that the superior friability results established by the examples in the present specification establish nonobviousness over Gantt *a fortiori*.

Nonobviousness of Claims 16, 27, and 33

The specification also contains comparative data showing the superior or unexpected hardness and/or friability of a compression blend or tablet containing colloidal silicon dioxide but substantially free of lubricant, further illustrating the nonobviousness of claims 16, 27, and 33. Applicants point to Examples 11-13 in the specification, which contain such a compression blend/tablet and exhibit high hardness (19.1-22.4 kP) and low friability (0.17%-0.25%). These results are significant because high hardness and low friability indicate resistance to chipping, abrasion, and breakage during transportation, storage, and handling.[28] In comparison, Example 3 (with ingredients identical to Examples 1 and 2 of Gantt) lacks colloidal silicon dioxide and includes a lubricant (magnesium stearate). Example 3 exhibits poor hardness (1 kP) and undeterminable friability (too friable to measure). (See Table 2 below.)

The comparative data in the specification establishes that a compressible blend or tablet incorporating colloidal silicon dioxide and substantially free of lubricants results in substantially superior hardness values (~20-fold improvement) and far superior friability values. Thus Applicants respectfully submit that the comparative data in the specification rebuts the Examiner's position that the tablets of instant claims 16, 27, and 33 are obvious.

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[28] Specification, pages 11-12, paras. [0029]-[0030].

Table 2:
Tablets with Colloidal Silicon Dioxide and Substantially Free of Lubricants
Compared to
Tablets without Colloidal Silicon Dioxide and Including a Lubricant

	Example 3	Example 11	Example 12*	Example 13*
Inner coating	ethylcellulose	ethylcellulose	ethylcellulose	ethylcellulose
Compressible coating: Plasticizer + Polymer	HPMC + PEG 400	ethylcellulose + diethylphthalate	ethylcellulose + diethylphthalate	ethylcellulose + diethylphthalate
Additional ingredients in compressible blend	MCC; Crospovidone; Mg stearate	Colloidal SiO_2; MCC; Crospovidone; Sodium lauryl sulfate	Colloidal SiO_2; MCC; Crospovidone	Colloidal SiO_2; MCC; Crospovidone
Hardness	1 kP	19.1 kP	22.4 kP	19.8 kP
Friability	Too friable to measure	0.17%	0.13%	0.25%

* Examples 12 and 13 contain the same ingredients but differ in their relative amounts.

Applicants point out that the tablet/compression blend of Example 3 contains the same ingredients as Examples 1 and 2 of Gantt, the primary reference cited by the Examiner (presumably what the Examiner apparently considers to be the closest prior art of record). Thus the comparison provided by the examples in the present specification are effectively a direct comparison to Gantt.

Therefore, Applicants submit that the comparative results of the present specification illustrating substantially superior friability and/or hardness establish the nonobviousness of the pending claims.

Applicants respectfully submit that the claims are now in condition for allowance, early notice of which would be appreciated. Should the Examiner disagree, Applicants respectfully request a telephonic or in-person interview with the undersigned attorney to discuss any remaining issues and to expedite the eventual allowance of the claims.

Except for issue fees payable under 37 C.F.R. 1.18, the Commissioner is hereby authorized by this paper to charge any additional fees during the entire pendency of this

application including fees due under 37 C.F.R. 1.16 and 1.17 which may be required, including any required extension of time fees, or credit any overpayment to Deposit Account 50-1283. This paragraph is intended to be a **CONSTRUCTIVE PETITION FOR EXTENSION OF TIME** in accordance with 37 C.F.R. 1.136(a)(3).

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Respectfully submitted,
COOLEY GODWARD KRONISH LLP

COOLEY GODWARD KRONISH LLP
CUSTOMER NUMBER 58249
ATTN: Patent Group
777 6th Street, NW, Suite 1100
Washington, DC 20001
Tel: (202) 842-7800
Fax: (202) 842-7899

By: Leigh Warren
Leigh M. Warren
Reg. No. 59,548